



FEB 23 2011

Mr. Marc Ullman, Esq.
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Re: Docket No. FDA-2009-P-0298

Dear Mr. Ullman:

This letter responds to the citizen petition that you submitted on June 29, 2009 on behalf of your client OVOS Natural Health Inc. (OVOS), requesting, among other things, that the Food and Drug Administration (FDA) determine whether homotaurine can be marketed as a dietary ingredient for use in dietary supplements.

In accordance with Title 21 of the Code of Federal Regulations (CFR), section 10.30(e)(3) (21 CFR 10.30(e)(3)), and for the reasons stated below, this letter is to advise you that FDA is denying your petition based on FDA's conclusion that homotaurine is not a dietary ingredient under section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act).

I. Procedural History

On June 29, 2009, you submitted the above-referenced citizen petition, under 21 CFR 10.30, requesting that the agency: (1) Promulgate a regulation pursuant to section 201(ff)(3)(B)(ii) of the FD&C Act (21 U.S.C. 321(ff)(3)(B)(ii)) "acknowledging that the use of OVOS' homotaurine dietary ingredient in dietary supplements is legal" under the FD&C Act;¹ or (2) Promulgate a regulation pursuant to section 301(l)(2) of the FD&C Act (21 U.S.C. 331(l)(2)) "acknowledging that FDA approves of the use of OVOS' homotaurine as a dietary ingredient for use in dietary supplements."²

¹ Section 201(ff)(3)(B)(ii) states that a dietary supplement does not include "an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter."

² Section 301(l) states that "[t]he introduction or delivery for introduction into interstate commerce of any food to which has been added a drug approved under section 505, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, [is prohibited] unless - ... (2) the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, approving the use of such drug or such biological product in the food."

In this citizen petition, you state that:

On August 23, 2002, BELLUS, the parent Company of OVOS, submitted an IND (No. 63,879) with the FDA for the study of homotaurine, an amino acid found in certain species of seaweed (kelp), for potential applications in the treatment of patients suffering from Alzheimer's disease. On May 22, 2008, BELLUS chose to voluntarily discontinue the pursuit of the IND following the completion of a 78-week Phase III North American study of homotaurine ... BELLUS through its incorporation of OVOS, has elected to pursue an alternate pathway to market for homotaurine as an ingredient for use in dietary supplements ... BELLUS is the former holder of the IND and the owner of all relevant intellectual property associated with homotaurine, and OVOS was created specifically for the purposes of commercializing homotaurine as a dietary supplement. As such, FDA should recognize that the provisions of both §201(ff) and §301(l) of the [FD&C Act] are designed to permit BELLUS, acting through its subsidiary, OVOS, and other similarly situated entities with a pathway to market for substances that, but for the existence of the IND, could otherwise legally be marketed for sale as an ingredient in dietary supplements.

In addition, on June 29, 2009, FDA received and filed a new dietary ingredient (NDI) notification submitted by OVOS pursuant to section 413(a)(2) of the FD&C Act (21 U.S.C. 350b(a)(2)) advising FDA of its intent to market homotaurine as a new dietary ingredient for use in dietary supplements. OVOS stated in its NDI notification that homotaurine is a dietary ingredient because it is an amino acid. You incorporated this notification into the petition by reference.

II. FDA's Response to the Citizen Petition

A. Summary of Decision

FDA has considered the information set forth in the petition, and concludes that your request must be denied based on FDA's conclusion, supported by overwhelming scientific opinion, that homotaurine is not a dietary ingredient under section 201(ff)(1). Specifically, OVOS' homotaurine is not an amino acid under section 201(ff)(1)(D) of the FD&C Act, nor does it fit under any of the other dietary ingredient categories listed in section 201(ff)(1). Because FDA concludes that OVOS' homotaurine is not a dietary ingredient, FDA concludes that your request that FDA exempt OVOS' homotaurine from the exclusion clause in section 201(ff)(3)(B)(ii) or from section 301(l) of the FD&C Act is moot. Therefore, your petition is denied.

B. Homotaurine is Not a Dietary Ingredient under the FD&C Act

Under section 201(ff)(1) of the FD&C Act, the term "dietary supplement" means "a product (other than tobacco) intended to supplement the diet that bears or contains one

or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentration, metabolite, constituent, extract, or combination of [any ingredient described above].”

As explained below, FDA has concluded that OVOS’ homotaurine is not a dietary ingredient because it does not fall within any of the categories of dietary ingredients listed in section 201(ff)(1)(A)-(F) of the FD&C Act.

1. Homotaurine is Not an “Amino Acid” under 201(ff)(1)(D)

OVOS states in its NDI notification that homotaurine is a dietary ingredient because it is an amino acid. However, as explained below, FDA has determined that homotaurine is not an amino acid under 201(ff)(1)(D). Specifically, FDA has concluded that for the purposes of section 201(ff)(1)(D) of the FD&C Act, the term “amino acid” refers to an *alpha*-amino carboxylic acid used as a constituent of proteins or peptides (hereinafter “proteins”). Homotaurine is a *gamma*-amino sulfonic acid. It is not an *alpha*-amino carboxylic acid or a constituent of proteins.

FDA interprets the categories of dietary ingredients listed in section 201(ff)(1), including amino acids, in light of the legislative history of the Dietary Supplement Health and Education Act of 1994 (DSHEA), which added the section defining dietary supplements to the FD&C Act. Congress enacted DSHEA after finding “a link between the ingestion of certain nutrients or dietary supplements” and various health benefits, emphasizing “the importance of nutrition and the benefits of dietary supplements to health promotion and disease prevention.”³

Thus, FDA concludes that nutrition science is the appropriate scientific context for analysis of what is an “amino acid” under section 201(ff)(1)(D) of the FD&C Act. The amino acids recognized in nutrition science are *alpha*-amino carboxylic acids, which are constituents of proteins. The Food and Nutrition Board of the Institute of Medicine (IOM) of the National Academies, which is a recognized authority on nutrition, describes “the amino acids that are incorporated into mammalian protein” as having “a carboxyl group, an amino nitrogen group, and a side chain attached to a central α -carbon” in its “Dietary Reference Intakes” report in the section entitled “Amino Acids.”⁴

The “Amino Acids” section of this IOM report discusses the twenty amino acids that are consistent with this definition. These amino acids do not include homotaurine. Many of these amino acids are essential nutrients and thus can only be supplied through

³ 140 Cong. Rec. S14798 (daily ed. Oct. 7, 1994) (statement of Sen. Feingold).

⁴ Food and Nutrition Board, National Institute of Medicine of the National Academies, “Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids,” (Washington DC, National Academies Press, 2005).

the diet.⁵ FDA's food additive regulation for amino acids used as "nutrients added to foods" (21 CFR 172.320) lists the same twenty individual amino acids.

Other government bodies, in the context of nutrition and dietary supplements, also define amino acids as a "chemical building block of protein" and as "constituents of proteins," which are *alpha*-amino carboxylic acids.⁶ The National Institutes of Health's (NIH) Office of Dietary Supplements defines amino acid as "a chemical building block of protein."⁷ The Natural Health Products Directorate of Health Canada defines amino acid as "a class of organic molecule that contains amino and carboxyl groups ... [which] form the main constituents of proteins."⁸

Further, the report, "Safety of amino acids used as dietary supplements," prepared for FDA's Center for Food Safety and Applied Nutrition (CFSAN) by the Federation of American Societies for Experimental Biology, when focusing on the nutritional and dietary role of amino acids, refers to amino acids as the "structural units of protein."⁹

Dictionary definitions of the term "amino acid" likewise support FDA's definition.¹⁰ Webster's II New Riverside Desk Dictionary defines amino acid as "an organic compound having both an amino group (NH₂) and a carboxylic acid group (COOH)" and any of a class of nitrogenous organic compounds that are essential components of proteins.¹¹ The Concise Oxford English Dictionary defines amino acids as "any of a class of about twenty organic compounds which form the basic constituents of proteins and contain both a carboxyl (COOH) and an amino (NH₂) group."¹² These definitions refer to amino acids as constituents of proteins, and, thus, also refer to *alpha*-amino carboxylic acids.

FDA recognizes that "amino acid" can be defined more broadly in other contexts. Some more general definitions rely on properties central to other scientific disciplines, such as organic chemistry. For example, one organic chemistry textbook states that "[t]he term amino acid might mean any molecule containing both an amino group and any type of acid group ..." (emphasis added).¹³ Nonetheless, this textbook states in the same sentence: "... however, the term is almost always used to refer to an α -amino

⁵ J. M. Berg, J. L. Tymoczko and L. Stryer, eds., Biochemistry, p 671, 5th edition, 2002, W.H. Freeman and Company.

⁶ All amino acids that are constituents of proteins are *alpha* amino acids because they have the carboxyl group linked to the *alpha* carbon of their carbon chain. J. M. Berg, J. L. Tymoczko and L. Stryer, eds., Biochemistry, pp 45, 51, 5th edition, 2002, W.H. Freeman and Company.

⁷ <http://ods.od.nih.gov/factsheets/BotanicalBackground-HealthProfessional/> (Accessed December 20, 2010).

⁸ Natural Health Products Directorate (NHPD), "Overview of the Natural Health Products Regulations Guidance Documents," November 2003.

⁹ S.A. Anderson, R.D., Ph.D., and D. J. Raiten, Ph.D., eds., "Safety of amino acids used as dietary supplements," July 1992.

¹⁰ See, *supra*, note 7.

¹¹ "Amino acid," Webster's II New Riverside University Dictionary, 1994, Houghton Mifflin Company.

¹² "Amino acid," Concise Oxford English Dictionary, 11th edition, revised, 2008, Oxford University Press.

¹³ L.G. Wade, Jr., Organic Chemistry, p 1154, 6th Edition, 2010, Pearson Education, Inc.

carboxylic acid” (emphasis added) - which, as discussed above, would exclude homotaurine. However, more general definitions that include chemical or other non-nutritive properties are not appropriate for the purpose of defining an “amino acid” in the context of the supplementation of the human diet.

In its NDI notification, OVOS argues that the definition of the term “amino acid” should be “compounds that include an amino group (NH₂) and an acidic function,” and that homotaurine is an amino acid according to this definition.¹⁴ In the NDI notification, OVOS uses the following references to support its position that homotaurine is an amino acid:

- (1) The “Economic Characterization of the Dietary Supplement Industry Final Report,”¹⁵ which includes a definition of amino acids as “compounds that include an amino group (NH₂) and an acidic function,” and describes taurine as an amino acid; and
- (2) The “Dietary Supplements Labels Database,”¹⁶ which lists taurine as an amino acid.

However, these references refer to taurine, not homotaurine, which is a separate compound with a different chemical structure.¹⁷ Unlike homotaurine, taurine is an end product of human amino acid metabolism and thus a metabolite of an amino acid.¹⁸ Taurine is not the subject of the request in the petition.

Furthermore, the purpose of the report and database is not to define “amino acid.” The “Economic Characterization of the Dietary Supplement Industry Final Report” was prepared by economists and market researchers at the Research Triangle Institute under contract to FDA to “collect information and report on the nature, size, and scope of the dietary supplement industry.” The report also states that “[n]early all information contained in this report was obtained from secondary data sources” and from interviews with various dietary supplement industry representatives. It does not purport to include any scientific, medical, or regulatory analysis of dietary supplements, nor does it include any citations for its terminology. The “Dietary Supplements Labels Database” prepared by NIH reproduces information from the labels that manufacturers used when marketing their products. Thus, if a company chooses to describe a substance on a label as an amino acid, it will be listed as such in the database. The limited purpose of the database is demonstrated by the introductory description of the database: “The Dietary Supplements Labels Database offers information about label ingredients in more than

¹⁴ As stated above, homotaurine is *gamma*-amino sulfonic acid.

¹⁵ Research Triangle Institute, “Economic Characterization of the Dietary Supplement Industry Final Report,” March 1999.

¹⁶ <http://dietarysupplements.nlm.nih.gov/dietary/> (Accessed February 7, 2011).

¹⁷ As indicated by the prefix “homo,” homotaurine has a carbon skeleton that is longer than that of taurine by one methylene group. K.J. Thurlow, Chemical Nomenclature, p. 177, 1998, Kluwer Academic Publishers.

¹⁸ Griffith, O.W., “Mammalian Sulfur Amino Acid Metabolism: An Overview,” Methods of Enzymology, 143: 366-76 (1987). Taurine is an end product of the metabolism of the amino acid cysteine.

three thousand selected brands of dietary supplements. It enables users to compare label ingredients in different brands.”¹⁹

For all these reasons, FDA has concluded that for the purposes of section 201(ff)(1)(D) of the FD&C Act, the term “amino acid” refers to an *alpha*-amino carboxylic acid used as a constituent of proteins. Homotaurine is a *gamma*-amino sulfonic acid. It is not an *alpha*-amino carboxylic acid or a constituent of proteins.

2. Homotaurine is Not a Dietary Ingredient under Any Other Category Listed in Section 201(ff)(1)

FDA has also considered the possibility that OVOS' homotaurine might be a dietary ingredient under one or more of the other categories of “dietary ingredients” listed in section 201(ff)(1) of the FD&C Act.

According to OVOS' NDI notification, homotaurine naturally occurs in some plants, including the seaweed dulse (*Rhodomenia palmate* (Linnaeus) Greville). However, OVOS' homotaurine is made synthetically (i.e., it is not extracted from *Rhodomenia palmate* or any other botanical) and thus is not a botanical under section 201(ff)(1)(C) of the FD&C Act.²⁰

FDA can find no evidence in the information you submitted, the information OVOS submitted to FDA in its NDI notification, or in a search of the relevant scientific literature, that OVOS' synthetically made homotaurine is a dietary ingredient under any of the other categories of “dietary ingredients” listed in section 201(ff)(1) of the FD&C Act. Homotaurine is not a vitamin, a mineral, an herb or other botanical, nor is there any evidence that it has ever been a dietary substance for use by man to increase the total dietary intake. Furthermore, homotaurine is not a concentrate, metabolite, constituent, extract, or combination of any ingredient described in sections 201(ff)(1)(A), (B), (C), or (E).

Therefore, FDA concludes that OVOS' synthetic homotaurine is not a “dietary ingredient” under section 201(ff)(1).

¹⁹ <http://dietarysupplements.nlm.nih.gov/dietary/> (Accessed February 7, 2011).

²⁰ FDA has previously stated that synthetic compounds are not botanicals under section 201(ff)(1). See, e.g., Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 FR 6788, 6793 (Feb. 11, 2004); Warning Letter from FDA to Scientifically Advanced Nutrition, Ref. No. 02-HFD-312-06, June 13, 2002.

III. Conclusion

Because FDA concludes that OVOS' homotaurine is not a dietary ingredient under 201(ff)(1), FDA concludes that your request that FDA exempt OVOS' homotaurine from the exclusion clause in section 201(ff)(3)(B)(ii) or from section 301(ll) of the FD&C Act is moot. Therefore, your requests that FDA promulgate regulations pursuant to sections 201(ff)(3)(B)(ii) and 301(ll)(2) for OVOS' homotaurine are denied.

Sincerely yours,

A handwritten signature in black ink that reads "Michael M Landa". The signature is written in a cursive, flowing style.

Michael M. Landa
Acting Director
Center for Food Safety
and Applied Nutrition